REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Restriction Requirement

Pursuant to the restriction requirement set forth in the Office Action dated June 6, 2003, applicants elected the invention of Group I, claims 1-15, drawn to a non-interacting drug combination. Additionally, pursuant to the Examiner's request for a single species, applicants *provisionally elected* fenofibrate as the specific "second drug" species, and *provisionally elected* the species wherein the drugs are administered together. Amended claims 1-15 were presented in accordance with the restriction requirement.

In the present Office Action, the Examiner notes "Applicant's election of fenofibrate as the second drug," and withdraws claims 7-10 and 13-15 from further consideration as being drawn to non-elected subject matter.

The provisionally non-elected subject matter of claims 7-10 and 13-15 has been maintained in this application, but indicated as presently withdrawn, so that this subject matter is available for examination as soon as the elected subject matter is found to be patentable. New claims 33-38 have been added, and will be discussed further below. Inasmuch as each of new claims 33-38 is dependent on one or more of the presently elected claims, it is respectfully submitted that these new claims are appropriate for examination together with the elected invention.

Claim Amendments

The claims have been amended in a manner which is believed to more clearly set forth the elected invention, and to more appropriately separate the product and method limitations. In summary:

- Claim 1 has been amended to clearly refer to a "first drug," being the specific HMG-CoA reductase inhibitor now know as rosuvastatin, and a "second drug," which is an inhibitor, inducer or substrate of P450 isoenzyme 3A4, as more particularly defined in the dependent claims.
- Claim 2 is unchanged.
- Claim 3 has been cancelled, since administering the drugs together or sequentially is more appropriately a method step. The substance of elected claim 3 has been carried into new method claims 35-37.
- Claim 4 has been amended to more clearly define the second drug in terms of its characteristic (cholesterol lowering drug) rather than its intended use. The provisionally elected second drug, fenofibrate, is a type of cholesterol lowering drug.
- Claim 5 lists specific cholesterol lowering drugs (including the provisionally elected fenofibrate), and has been amended herein to update applicants' preferences. Support for this claim and its amendment is found in the specification at page 6, lines 19-22.
- Claim 6 is not further amended herein, and is directed to the second drug being fenofibrate, the provisionally elected species.

- Claims 7-10 have been withdrawn by the Examiner as being directed to other types of "second drug" not encompassing the provisionally elected fenofibrate. These claims have been designated as "withdrawn" above, but maintained in this application for rejoinder when the provisionally elected subject matter is found allowable.
- Original elected dependent claim 11 provided the amount of the first drug dosed once per day. Claim 11 has been cancelled and its subject matter more clearly expressed in new method claim 38.
- Elected claim 12 is directed to a pharmaceutical formulation comprising the non-interacting drug combination of claim 1 together with a pharmaceutically acceptable diluent, carrier or adjuvant. The above amendment simplifies claim 12 by not repeating the definition of the first and second drugs, which definitions are brought into this claim by its dependence on claim 1.
- Claims 13-15 have been withdrawn by the Examiner as being directed to other types of "second drug" not encompassing the provisionally elected fenofibrate. These claims have been designated as "withdrawn" above, but maintained in this application for rejoinder when the provisionally elected subject matter is found allowable.
- Claims 16-32 were previously cancelled.

New claims 33-38 have been added to claim pharmaceutical compositions comprising the elected non-interacting drug combination, and methods of treatment using such non-interacting drug combination. Inasmuch as these added claims are all dependent on presently elected claims, it is believed that they are appropriately

considered together therewith. Nevertheless, if the Examiner considers any one or more of these new claims to be outside of the provisionally elected invention, it is respectfully requested that these claims be entered but denominated as withdrawn so that they can be easily rejoined at an appropriate time, after the provisionally elected subject matter is found allowable.

- New claim 33 is a pharmaceutical composition claim dependent on elected claim 1, wherein the non-interacting drug combination of claim 1 is in the form of a pharmacy pack comprising the first drug and the second drug as separate dosage forms. Support for "pharmacy pack" is found, *e.g.*, at page 5, lines 13-15 and in the original claims, and support for the first and second drugs being in separate dosage forms is found, *e.g.*, at page 27, lines 22-29.
- New method claim 34 is directed toward treating "hypercholesterolaemia or mixed hyperlipidaemia " by administering an effective amount of the pharmaceutical formulation of elected claim 12, in which the first and second drugs are combined in a single unit dose with a pharmaceutically-acceptable diluent, carrier or adjuvant. Support for this claim is found in the specification, *e.g.*, at page 24, line 22 through page 25, line 17.
- New method claim 35 is directed toward treating "hypercholesterolaemia or mixed hyperlipidaemia " by administering an effective amount of the first drug and an effective amount of the second drug, as claimed in elected claim 1. Support for this claim is found in the specification, *e.g.*, at page 24, line 22 through page 25, line 17.

- Method claim 36 is dependent on claim 35, and provides that the first and second drugs are administered simultaneously. Support for the simultaneous administration of the first and second drugs is found in the specification, *e.g.*, at page 27, lines 22-29.
- Method claim 37 is also dependent on claim 35, and provides that the first and second drugs are administered sequentially. Support for the sequential administration of the first and second drugs is found in the specification, *e.g.*, at page 27, lines 22-29.
- Method claim 38 is dependent on method claims 34-37, and provides for the HMG-CoA reductase inhibitor dosing regimen originally set forth in elected, now cancelled, claim 11.

For these reasons set forth above, it is respectfully requested that the foregoing amendments be entered.

Claim Rejections – 35 USC § 103

Claims 1-6, 11 and 12 have been rejected under 35 USC § 103 as being unpatentable over six cited references. Since the references each teach that the individual components of the claimed composition are known in the art to be used for the same purpose, the Examiner asserts that it would be *prima facie* obvious to combine them into a single composition. This ground for rejection of the present claims is respectfully traversed.

As detailed further below, long recognized adverse drug interactions between HMG-CoA reductase inhibitors (statins) and another drug which is an inhibitor, inducer

or substrate of P450 isoenzyme 3A4, have led to the inclusion of warnings or contraindications of such drug combinations in the literature and approved labels of commercial statin drugs (see, *e.g.*, specification at page 3, lines 20-23).[1] Thus, contrary to the Examiner's assertion, at the time of applicants invention the art *taught away from* the combination or coadministration of second drugs of the type recited in the present claims with statins. It will further be shown below that this was particularly the case where the second drug was a cholesterol lowering agent such as the drugs listed in present claim 5.

However, applicants found that the particular (recently commercialized) statin named in the present claims[2] was not significantly involved in the P450 isoenzyme 3A4 metabolic pathway, and thus does not cause clinically significant drug interactions with such "second drugs" through the mechanism of cytochrome P450 isoenzyme 3A4 drug metabolism. See, *e.g.*, specification page 4, lines 13-30 and the Experimental section extending from page 8, line 23 through page 11, line 9. See, also, Williams (2002) at page 360 [more completely identified below], which reports that with the new statin, rosuvastatin, there was "no evidence of clinically relevant liver function abnormalities or myopathy," and that cited authors [in publications dated *after* the present invention] "concluded that rosuvastatin metabolism is likely to be limited *in vivo* and that clinically significant metabolic interactions are unlikely to occur."

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[1] See, also, Williams (2002) [more fully identified below], Table IV at page 353, noting warnings regarding possible drug interactions with HMG-CoA reductase inhibitors, contained in Recommendations in European summaries of product characteristics.

[2] The compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid is now known as rosuvastatin, and rosuvastatin calcium was recently approved and commercialized under the brand name CRESTOR®.

Documents Attached in Support of Discussion

The following additional publications are submitted herewith in support of the discussion below:

Referred to as:	**Publication:**
Hunninghake (1992)	Hunninghake D. HMG CoA reductase inhibitors. Current Opinion in Lipidology 1992; 3:22-28 (cited in the specification at page 3, lines 11-12).
Miller (1998)	Miller D, Spence J. Clinical Pharmacokinetics of Fibric Acid Derivatives (Fibrates). Clin Pharmacokinet 1998 Feb; 34(2): 155-162.
Williams (2002)	Williams D, Feely J. Pharmacokinetic-Pharmacodynamic Drug Interactions with HMG-CoA Reductase Inhibitors. Clin Pharmacokinet 2002; 41(5): 343-370.

The Present Claims are Not Prima Facia Obvious

The present invention is directed to a "non-interacting drug combination" comprising a "first drug," which is the HMG-CoA reductase inhibitor now known as rosuvastatin, and a "second drug," which is "an inhibitor, inducer or substrate of P450 isoenzyme 3A4."

As discussed in the specification paragraph bridging pages 3 and 4, nearly all drugs are metabolized to some degree in the human, generally to a less lipid soluble compound which is more easily excreted by the kidney or in liver bile. Cytochrome P450 (CYP) represents a major class of drug metabolizing enzymes and exists as a family of isoenzymes found in hepatic microsomes. Six specific P450 isoenzymes are responsible for the metabolism of most of the commonly used drugs, namely P450 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Within the CYP system, the 3A4 isoenzyme (or CYP3A4) is the most abundant metabolic pathway, constituting some 30% of total CYP activity, and is

responsible for the oxidative metabolism of more than 50% of drugs used in humans. (Williams (2002) at 355, column 2).

Where two drugs, which are inhibitors, inducers or substrates of P450 isoenzyme 3A4, are coadministered, there is a significant possibility of an adverse drug interaction. Thus, for example, where the metabolism of a statin is to a significant degree mediated by CYP3A4, the coadministration of another drug which is itself an inhibitor or substrate of CYP3A4 can impair the metabolism of the statin and result in a many-fold increase in its concentration to toxic levels. In the same manner, involvement of the statin in the CYP3A4 metabolic pathway can similarly affect the "second drug." See, *e.g.*, the specification discussion at page 2, line 10 through page 4, line 11; Hunninghake (1992) at 24, column 2; Miller (1998) at 159, columns 1 and 2; and Williams (2002) at 354, column 2 *et seq.*

By at least 1992, fibric acid derivatives (fibrates) were the second most commonly used class of lipid-lowering drugs, after HMG-CoA reductase inhibitors. Hunninghake (1992) at 24. As of that time, however, Hunninghake noted that a combination of an HMG-CoA reductase inhibitor with either niacin or fibric acid would more effectively control patients having an abnormal level of lipids, total and LDL cholesterol and triglycerides, but cautioned that "such combinations increase the risk of myositis and rhabdomyolysis." Hunninghake (1992) at 24. Miller *et al.* further emphasize that a principal cause of drug interactions with fibrates is that CYP3A4 is required for the metabolism of all members of this class of drugs, and that any other drug that modifies the activity of CYP3A4 or itself requires CYP3A4 for its metabolism can be affected by the simultaneous administration of a fibrate. Miller (1998) at 158. This risk

of adverse drug interactions between coadministered fibrates and HMG-CoA reductase inhibitors is specifically discussed by Miller *et al.* at page 159.

Williams (2002) more broadly confirms the risk of serious interaction with HMG-CoA reductase inhibitors. For instance, Williams *et al.* note that the risk of serious interaction causing myopathy is enhanced when statin metabolism is markedly inhibited, thus increasing plasma concentration of the drug and lengthening exposure to it, and that the interaction potential of the various statins varies considerably, "probably as a result of a different role of CYP3A4 in their transformation. Williams (2002) at 356, citing two 1997 literature references. Also see, generally, the discussion of under section 3.3 Hepatic Metabolism (pages 354-355) and the discussion under section 3.3.1 Statins and the Cytochrome P450 System and under sections 3.3.2 through 3.3.7 relating to drug interactions of specific commercial statins known at the time of applicants' invention (pages 355-360).

Thus it is clear that the art as a whole, at about the time of applicants' invention taught against the coadministration statins in general with any other drug which is an inhibitor, inducer or substrate of P450 isoenzyme 3A4, particularly fibrates including fenofibrate. Each of the present claims recites a "non-interacting drug combination," which is defined in the specification at page 5, lines 29-31 as meaning:

> ...a drug combination for which there is no adverse affect to the patient by the administration through the mechanism of drug metabolism by cytochrome P450 isoenzyme 3A4.

Each of the claims also identifies the "second drug" of the combination as being "an inhibitor, inducer or substrate of P450 isoenzyme 3A4, which the prior art taught against coadministering with an HMG CoA reductase inhibitor. Therefore, applicants' claimed

"non-interacting drug combination" of such a second drug with the specific HMG CoA reductase inhibitor, rosuvastatin, was contrary to the state of the art when the invention was made. It is thus respectfully submitted that the "non-interacting" combination of the first and second drugs as presently claimed by applicants, being *contrary* to the understanding and teaching in the art, refutes or overcomes the *prima facie* obviousness assertion of the Examiner.

It is respectfully submitted that the "non-interacting" combination of the first and second drugs as presently claimed by applicants, being *contrary* to the understanding and teaching of the art, refutes or overcomes the *prima facie* obviousness assertion of the Examiner.

Conclusion

In view of the above amendments and the foregoing remarks, supported by the relevant literature, it is respectfully submitted that any assertion of *prima facie* obviousness, if any was justified, has been overcome. Accordingly, the allowance of all claims (including the withdrawn claims after rejoinder) is believed to be in order, and is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: March 10, 2004 By: _____

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